

WHAT IS CLAIMED IS:

1. A method of specifically delivering a diagnostic or therapeutic agent to a VEGFR1-
5 expressing cell, comprising:

(a) providing an immunoconjugate comprising said diagnostic or therapeutic agent
operatively attached to at least a first anti-VEGF antibody, or antigen-binding
fragment thereof, that binds to substantially the same epitope as the monoclonal
10 antibody 2C3 (ATCC PTA 1595); and

(b) exposing said immunoconjugate to a cell population that comprises VEGFR1-
expressing cells that have VEGF bound thereto, thereby delivering said
diagnostic or therapeutic agent to said VEGFR1-expressing cells.
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2. A method for delivering a diagnostic or therapeutic agent to a vascularized tumor,
comprising administering to an animal with a vascularized tumor a biologically effective
amount of a composition comprising an immunoconjugate in which said diagnostic or
20 therapeutic agent is operatively attached to an anti-VEGF antibody, or antigen-binding
fragment thereof, that binds to substantially the same epitope as the monoclonal antibody 2C3
(ATCC PTA 1595).

25 3. The method of claim 2, wherein said immunoconjugate binds to VEGF bound to
VEGFR1 expressed by endothelial cells of the vasculature of said vascularized tumor.

4. The method of claim 2, wherein said immunoconjugate binds to VEGF bound within
30 the stroma of said vascularized tumor.

5. A method for treating cancer, comprising administering to an animal that has a
vascularized solid tumor, a metastatic tumor or metastases from a primary tumor, a
35 therapeutically effective amount of at least a first pharmaceutical composition comprising at

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least a first immunoconjugate that comprises at least a first therapeutic agent operatively attached to at least a first anti-VEGF antibody, or antigen-binding fragment thereof, that binds to substantially the same epitope as the monoclonal antibody 2C3 (ATCC PTA 1595).

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6. The method of claim 5, wherein said at least a first antibody of said immunoconjugate is a monoclonal antibody or an antigen-binding fragment thereof.

10 7. The method of claim 5, wherein said at least a first antibody of said immunoconjugate is an scFv, Fv, Fab', Fab, diabody, linear antibody or F(ab')₂ antigen-binding fragment of an antibody.

15 8. The method of claim 5, wherein said at least a first antibody of said immunoconjugate is a human, humanized or part-human antibody or antigen-binding fragment thereof.

20 9. The method of claim 5, wherein said at least a first antibody of said immunoconjugate is a chimeric antibody or a recombinant antibody.

10. The method of claim 5, wherein said at least a first antibody of said immunoconjugate comprises at least a first variable region that includes an amino acid sequence region having
25 the amino acid sequence of SEQ ID NO:7 or SEQ ID NO:9.

11. The method of claim 5, wherein said at least a first antibody of said immunoconjugate is the monoclonal antibody 2C3 (ATCC PTA 1595).

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12. The method of claim 5, wherein said immunoconjugate comprises said at least a first antibody operatively attached to two or more therapeutic agents.

13. The method of claim 5, wherein said immunoconjugate comprises said at least a first antibody operatively attached to at least a first chemotherapeutic agent, radiotherapeutic agent, anti-angiogenic agent, apoptosis-inducing agent, steroid, antimetabolite, anthracycline, vinca
5 alkaloid, anti-tubulin drug, antibiotic, cytokine, alkylating agent or coagulant.

14. The method of claim 13, wherein said immunoconjugate comprises said at least a first antibody operatively attached to a cytotoxic, cytostatic or anticellular agent capable of killing or
10 suppressing the growth or cell division of endothelial cells.

15. The method of claim 14, wherein said immunoconjugate comprises said at least a first antibody operatively attached to a plant-, fungus- or bacteria-derived toxin.
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16. The method of claim 15, wherein said immunoconjugate comprises said at least a first antibody operatively attached to ricin A chain, deglycosylated ricin A chain, a ribosome inactivating protein, α -sarcin, gelonin, aspergillin, restrictocin, a ribonuclease, an
20 epipodophyllotoxin, diphtheria toxin or *Pseudomonas* exotoxin.

17. The method of claim 13, wherein said immunoconjugate comprises said at least a first antibody operatively attached to an anti-angiogenic agent.
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18. The method of claim 17, wherein said immunoconjugate comprises said at least a first antibody operatively attached to angiopoietin-2, angiostatin, vasculostatin, canstatin or maspin.
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19. The method of claim 17, wherein said immunoconjugate comprises said at least a first antibody operatively attached to endostatin.

20. The method of claim 13, wherein said immunoconjugate comprises said at least a first antibody operatively attached to an anti-tubulin drug.

5 21. The method of claim 20, wherein said immunoconjugate comprises said at least a first antibody operatively attached to an anti-tubulin drug selected from the group consisting of colchicine, taxol, vinblastine, vincristine, vindesine and a combretastatin.

10 22. The method of claim 13, wherein said immunoconjugate comprises said at least a first antibody operatively attached to a coagulant.

15 23. The method of claim 22, wherein said immunoconjugate comprises said at least a first antibody operatively attached to Tissue Factor, a human Tissue Factor, a mutant Tissue Factor deficient in the ability to activate Factor VII, truncated Tissue Factor or to a dimeric, trimeric or polymeric Tissue Factor, truncated Tissue Factor or Tissue Factor derivative.

20 24. The method of claim 5, wherein said immunoconjugate comprises said at least a first antibody operatively attached to at least a first indirect therapeutic agent that cleaves a substantially inactive prodrug to release a substantially active drug.

25 25. The method of claim 5, wherein said immunoconjugate comprises said at least a first antibody operatively attached to said at least a first therapeutic agent as a fusion protein prepared by expressing a recombinant vector that comprises, in the same reading frame, a DNA segment encoding said antibody operatively linked to a DNA segment encoding said therapeutic agent.

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26. The method of claim 5, wherein said immunoconjugate comprises said at least a first antibody attached to a second antibody, or antigen binding region thereof, that binds to said at least a first therapeutic agent.

27. The method of claim 5, wherein said immunoconjugate comprises said at least a first antibody operatively attached to said at least a first therapeutic agent via a biologically
5 releasable bond or selectively cleavable linker.

28. The method of claim 27, wherein said immunoconjugate comprises said at least a first antibody operatively attached to said at least a first therapeutic agent via a peptide linker that
10 includes a cleavage site for urokinase, pro-urokinase, plasmin, plasminogen, TGF β , staphylokinase, Thrombin, Factor IXa, Factor Xa, a metalloproteinase, an interstitial collagenase, a gelatinase or a stromelysin.

29. The method of claim 5, wherein said at least a first pharmaceutical composition is administered to said animal intravenously.

30. The method of claim 5, further comprising subjecting said animal to radiotherapy.

31. The method of claim 5, further comprising administering to said animal a therapeutically effective amount of at least a second anti-cancer agent.

32. The method of claim 31, wherein said at least a second anti-cancer agent is administered to said animal simultaneously with said at least a first pharmaceutical composition.

33. The method of claim 31, wherein said at least a second anti-cancer agent is administered to said animal sequentially to said at least a first pharmaceutical composition.

34. The method of claim 31, wherein said at least a second anti-cancer agent is a chemotherapeutic agent, radiotherapeutic agent, anti-angiogenic agent, apoptosis-inducing agent or anti-tubulin drug or a prodrug or tumor-targeted form thereof.

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35. The method of claim 34, wherein said at least a second anti-cancer agent is angiopoietin-2, endostatin, angiostatin, vasculostatin, canstatin, maspin, colchicine, taxol, vinblastine, vincristine, vindesine, a combretastatin, or a prodrug or tumor-targeted form thereof.

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36. The method of claim 31, wherein said at least a second anti-cancer agent is a targeting agent-therapeutic agent construct comprising a therapeutic agent operatively linked to at least a first targeting region that binds to an accessible component of a tumor cell or tumor stroma or to a surface-expressed, surface-accessible, surface-localized, cytokine-inducible or coagulant-inducible component of tumor vasculature or intratumoral vasculature.

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37. The method of claim 36, wherein said at least a first targeting region is operatively linked to a cytotoxic agent, anti-angiogenic agent, apoptosis-inducing agent or anti-tubulin drug.

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38. The method of claim 36, wherein said at least a first targeting region is operatively linked to Tissue Factor, truncated Tissue Factor or a Tissue Factor derivative or to an antibody, or antigen-binding fragment thereof, that binds to Tissue Factor, truncated Tissue Factor or a Tissue Factor derivative.

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39. The method of claim 31, wherein said at least a second therapeutic agent is a substantially inactive prodrug that is cleavable to form a substantially active drug.

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40. The method of claim 5, wherein:

(a) said at least a first antibody of said immunoconjugate is operatively attached to at least a first cleavage agent or enzyme and wherein said immunoconjugate targets said cleavage agent or enzyme to the tumor vasculature or stroma; and wherein

(b) at least a first substantially inactive prodrug is subsequently administered to said animal, wherein said prodrug is cleaved by said cleavage agent or enzyme to form a substantially active drug within said tumor vasculature or stroma.

41. The method of claim 40, wherein said first cleavage agent or enzyme and substantially inactive prodrug are operably matched agents selected from the groups consisting of:

(a) alkaline phosphatase, arylsulfatase, serratia protease, thermolysin, subtilisin, a carboxypeptidase, a cathepsin, D-alanylcarboxypeptidase, β -galactosidase, neuraminidase, β -lactamase, penicillin amidase and cytosine deaminase; and

(b) a phosphate-containing prodrug, sulfate-containing prodrug, peptide-based prodrug, D-amino acid-modified prodrug, glycosylated prodrug, β -lactam-containing prodrug, optionally substituted phenoxyacetamide- or phenylacetamide-containing prodrug and 5-fluorocytosine.

42. The method of claim 5, wherein said animal is a human patient.

43. A method for treating an animal with a vascularized solid tumor, comprising administering to said animal at least a first pharmaceutical composition that comprises at least a first immunoconjugate that comprises at least a first therapeutic agent operatively attached to at least a first anti-VEGF antibody, or antigen-binding fragment thereof, that binds to substantially the same epitope as the monoclonal antibody 2C3 (ATCC PTA 1595) and that inhibits VEGF-mediated angiogenesis and VEGF survival functions by significantly inhibiting VEGF binding to the VEGF receptor VEGFR2 (KDR/Flk-1).

44. A method for treating cancer, comprising administering to an animal with a vascularized tumor a therapeutically effective amount of at least a first pharmaceutical composition that comprises at least a first immunoconjugate that comprises at least a first therapeutic agent operatively attached to at least a first anti-VEGF antibody that binds to substantially the same epitope as the monoclonal antibody 2C3 (ATCC PTA 1595), or antigen-binding fragment thereof; wherein the antibody portion of said immunoconjugate significantly inhibits VEGF binding to the VEGF receptor VEGFR2 (KDR/Flk-1) without significantly inhibiting VEGF binding to the VEGF receptor VEGFR1 (Flt-1), thereby delivering said therapeutic agent to said vascularized tumor, inhibiting angiogenesis within said vascularized tumor and not significantly impairing macrophage-mediated anti-tumor responses within said vascularized tumor.

45. A method for treating cancer, comprising administering to an animal with a vascularized tumor a therapeutically effective amount of at least a first pharmaceutical composition that comprises at least a first immunoconjugate that comprises at least a first therapeutic agent operatively attached to at least a first anti-VEGF antibody that binds to substantially the same epitope as the monoclonal antibody 2C3 (ATCC PTA 1595), or antigen-binding fragment thereof; wherein the antibody portion of said immunoconjugate significantly inhibits VEGF binding to the VEGF receptor VEGFR2 (KDR/Flk-1) without significantly inhibiting VEGF binding to the VEGF receptor VEGFR1 (Flt-1), thereby delivering said therapeutic agent to said vascularized tumor, inhibiting angiogenesis within said vascularized tumor and not significantly inhibiting VEGF stimulation of macrophages, osteoclasts or chondroclasts within said animal.

46. A method for treating cancer, comprising administering to an animal that has a vascularized solid tumor:

5 (a) a first composition comprising at least a first immunoconjugate that comprises at least a first cleavage agent or enzyme operatively attached to at least a first anti-VEGF antibody, or antigen-binding fragment thereof, that binds to substantially the same epitope as the monoclonal antibody 2C3 (ATCC PTA 1595), thereby localizing said immunoconjugate to the vasculature or stroma of said vascularized solid tumor; and

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(b) subsequently administering to said animal a second composition that comprises at least one substantially inactive prodrug that is cleaved by the cleavage agent or enzyme attached to said antibody in said first composition, thereby releasing a substantially active drug specifically

15 within the vasculature or stroma of said vascularized solid tumor.